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# THE USE OF MODAFINIL IN OPERATIONAL SETTINGS : INDIVIDUAL DIFFERENCES IMPLICATIONS

**Dr Didier LAGARDE**

Médecin en Chef, Institut de Médecine Aérospatiale du Service de Santé des Armées  
B.P. 73  
91223 Brétigny sur Orge Cedex  
France

## • ABSTRACT

Disruptions in wake-sleep rhythms, particularly induced by SUSOPS and CONOPS, are limiting factors for military personnel in operation. Pharmacological aids, such as hypnotic or stimulant substances can be effective countermeasures. Modafinil (MODIODAL®, PROVIGIL®) is a synthetic molecule prescribed for the treatment of narcolepsia and idiopathic hypersomnia. The wakening effect is potent : modafinil allows healthy volunteers to stay awake and efficient for more than 60 hours, without side effects. Its mechanism of action is complex, and it could induce wakefulness by different mechanisms, as compared with other classical vigilance enhancing drugs such as amphetamines. A neuroprotective effect against neurotoxic organophosphate agents was recently discovered. Modafinil seems to be a powerful and safe countermeasure in the management of sleep-wake rhythm during operational situations.

## • INTRODUCTION

The use of drugs in sleep-wakefulness management during operational settings is changing a lot according to the fast development of new generation of psychotropics. During the second world war, the use of amphetamines was widely spread in the military personal, especially US army (16). Later during Falklands conflict, benzodiazepines were used, in a controlled maner, by the pilots of the Royal Air Force (13).

During the Persic Gulf war, a new and original substance, called modafinil, was used for the first time by french military personal under a very strict medical control (while american military personal used dexedrine) (5). Before the presentation of modafinil properties, we will see why we have to use a stimulant and what kind of stimulant to use.

## • THE CHOICE OF A STIMULANT

The choice of a psychotrop and especially of a stimulant to manage the vigilance come from the antinomia between physiological requirements and operational requirements.

Globally, each subject must respect his own quota of sleep, his own sleep type and his circadian rhythms. Generally, most people need between seven and eight

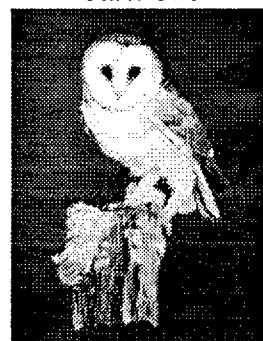
hours of sleep. But some of them, sleep five hours or ten hours ; we called them small and big sleepers and it is an inborn characteristic. The specific type of sleep is also a physiological requirement. Some people are morningness type, it is to say that they are very operational during the morning and are out of order after 10 p.m.. We called them "skylark". On another hand, some people are eveningness type, they have the maximum of their capacity in the evening and are able to stay available and efficient very late, but they can not awake up early in the morning. We called them "barn-owl".

## SPECIFIC TYPES



*skylark*

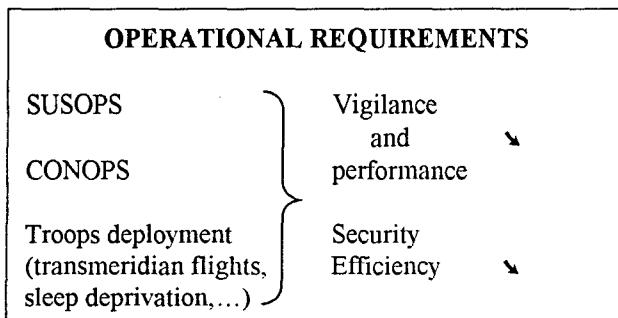
*barn-owl*



The result of circadian propensity to drowsiness is also very important. Everybody has two pics of drowsiness, one during the day located just after the lunch in a post-meridian period, the other during the night between 02 a.m. and 06 a.m. in the early morning. At the opposite, during the morning, around 10 a.m. and in the

afternoon between 6 p.m. and 10 p.m., we have a top level of vigilance. This daily fluctuation is found again with the level of performance (cognitive, psychomotor and physical performance). If we repeat all these physiological requirements, we will have the maximum of efficiency.

But the problem is induced by operational requirements. During sustained operations (SUSOPS) it is impossible for the soldier to sleep, sometimes during one or two consecutively days. During continuous operations (CONOPS) the soldier can sleep but not in a usual way, it is to say sometimes during the day and not during the night, sometimes two or three hours *i.e.* a disrupted sleep, and sometimes in a disturbed environment (noise, heat, light, etc...) This operational environment induces a decrease in vigilance and performance levels with fatigue, which can provoke a dramatically decrease of security and efficiency :



To help the subject to maintain a good level of vigilance and performance and to preserve his security, some counter measures must be proposed. Some of them concern the physiological management with recommendations about how to take a nap or what kind of meal to eat. Others concern pharmacological management and are used when the previous one are inefficient or inapplicable. It could be substances to induce sleep (hypnotics) or substances to prolonge wakefulness.

#### • THE CHOICE OF AN ORIGINAL SUBSTANCE

To prolonge wakefulness, as to induce sleep, we follow a pharmacological concept which presents three main points :

- this substance has to preserve the subject from deleterious effects of sleep disturbancies,
- it can be easy to use,
- the administration of this substance has not to induce side effects.

For these reasons, we eliminate drugs with side effects as amphetamines and amphetamine-like substances and also caffeine solution in case of repeated administration with a dose superior to 600 mg. The choice was given to a new and original wakening substance called modafinil (MODIODEL® or PROVIGIL®) studied in our laboratory since 1981 and classed by Jouvet (2) as an

eugregorius substance (in grec : *eu* = good and *gregor* = wakefulness).

#### • THE MAIN PROPERTIES OF MODAFINIL

##### - Indications

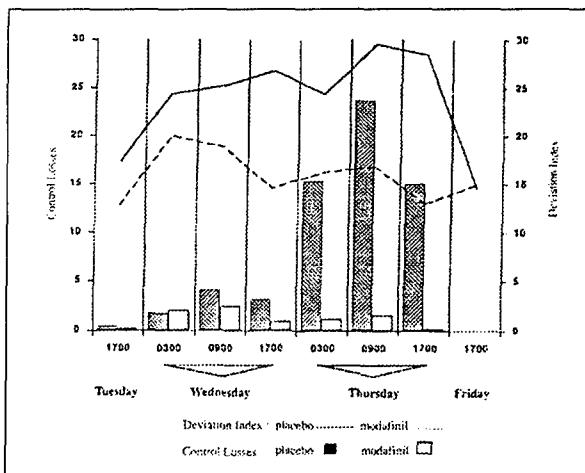
Modafinil = (diphenyl-methyl) sulfinyl-2-acetamide is a vigilance enhancing drug indicated in the treatment of narcolepsia and idiopathic hypersomnia. It is synthetized by L. LAFON laboratory (France).

##### - In human healthy subjects (all references are in 15)

Modafinil was also used in human healthy subjects as control population for the study of the interest of the substance in narcoleptic people : Benoit *et al.* (1987), Goldenberg *et al.* (1987), or as healthy people submitted to a sleep deprivation period : Puech and Bensimon (1987), Saletu *et al.* (1989), Lagarde *et al.* (1993, 1995a, 1995b, 1997, 1999), Bourdon *et al.* (1994), Pigeau and Buguet (1995).

##### - The awakening property

Modafinil presents a strong awakening effect during 60 hours of sleep deprivation. The performance is maintained at the same level than in reference period during 48 hours :



Comparative changes in performance at the tracking test under placebo and modafinil (from 7)

No side effect was found when a correct dose (200 mg) was administered every eight hours. One of the most interesting characteristic of modafinil is that it is not an anti-sleep substance but a vigilance enhancing drug. It is to say that it is possible to sleep, when the environment is available even if you took a pill, one or two hours before (3, 8). During a sleep deprivation period, this substance deletes microsleeps on EEG, increases the sleep latency (compared to placebo) and maintains the cognitive and psychomotor performance.

##### - The neuroprotective effect

We examined the neuroprotective effect of modafinil agonist soman-induced hippocampus damage. In mice, modafinil administered at 600 mg.k<sup>-1</sup> i.p. 2 hours before

soman significantly reduced the density of hippocampus  $\omega_3$  peripheral benzodiazepine binding sites, an indirect marker of neuronal damage, as compared to soman control animals. This was confirmed in rats (10). Similar results were found by another team on cerebral cortical cultures (1).

#### • AN ORIGINAL MECHANISM OF ACTION

The mechanism of action of modafinil is original and complex. Studies realized showed that modafinil acts as an agonist of  $\alpha_1$ -adrenergic post-synaptic receptors (4). It binds to the dopamine uptake carrier site with low affinity (12). At high doses, pimozide can partially antagonize the behavioral and EEG effects of modafinil (6). It increases turn-over of serotonin in striatum (14), decreases cortical inhibitory aminoacids (glycin) outflow (14). It increases intracellular and decreases extracellular level of excitatory aminoacids (aspartate and glutamate), and also increases energetic pool (creatine/phosphocreatine) and decreases metabolic amino acids (14). Lin *et al.* in 1996 (11) showed that modafinil could act upon anterior hypothalamus nucleus.

To summarize it is possible to say that the  $\alpha_1$ -adrenergic post-synaptic effects seem to be prominent ; at high doses, dopaminergic effects seem to appear. Moreover (at high doses) aminoacids neurotransmission system seems to be involved. Brain energetic effect could participate in the pharmacological action.

#### • THE USED PROPOSALS

Concerning only the wakening property, two kinds of attitudes are or could be adopted. In peace time : no drug must be used included training period ; the management of people must not include drug administration. One exception is the crash of helicopter or plane : to facilitate the waiting period between crash and rescue, modafinil is available in the kit located under the seat of the pilot. Like that the ejected pilot can stay awake two days to wait for the rescue.

In war time, the order to use modafinil is only given by the high command, the health service gives only advices. The directions for use depend of the operational situation and are confidential.

Concerning the individual differences implications, in healthy subjects we never found differences related to age or gender, but the differences observed concern the weight and sometimes individual susceptibility (9). To avoid these differences, a test could be done, starting with one pill (100 mg), then trying two pills (200 mg).

#### • CONCLUSION

Nowadays, SUSOPS and CONOPS are, unfortunately, spread all over the world. The respect of the soldier's physiology, to maintain his vigilance and performance but also his security, seems to be now taken into account ; the operational sleep management is more and more employed, because of new compounds as modafinil easy

to take, very powerful and very safe. Nevertheless, their use has to be under control.

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